MODELING LOCALIZED TURBULENT BLOOD FLOW IN ATHEROSCLEROTIC ARTERY LEADING TO PLATELET ACTIVATION

I. Haq and L. T. Al-Kury

Computational Modeling Research (CMR) Lab., Abu Dhabi, UAE

Email: ihaq31@yahoo.com, lina_kury@yahoo.com

Abstract-**Coronary heart disease (CHD) is caused by the build-up of plaque in the inner walls of the coronary arteries, restricting blood supply to the heart. Through computer modeling and simulation, we investigated the blood flow dynamics at the plaque region. Numerical solution of 2D Navier-Stokes equation (NSE) was obtained using finite element technique. Results show that under certain conditions, the blood flow becomes turbulent and hence induces localized stress regions 'hot-spots'. Highest stress values were at the plaque boundaries which may act as precursor to platelet activation and their subsequent aggregation. Understanding the initial events underlying atherosclerotic plaque growth may provide important information for developing new strategies to prevent CHD in the future.**

***Keywords*- coronary heart disease, computer modeling and simulation, blood flow dynamics, Navier-Stokes equation (NSE), turbulence, platelets, atherosclerotic plaque.**

I. INTRODUCTION

Atherosclerosis is the process by which cholesterol and other substances are deposited in the inner walls of the coronary arteries. This accumulation bulges into the interior of the arteries, obstructing blood flow to the heart and consequently leading to coronary heart disease (CHD) [1]. Platelets are known to be involved in the development of pathological thrombus at the atherosclerotic plaque region [2]. The thrombus usually occurs because of the direct contact of the plaque with the flowing blood. The plaque presents an unsmooth surface to the blood and therefore platelets begin to adhere to it. In addition, fibrin begins to deposit and red blood cells become entrapped to form a clot that gradually grows until it occludes the vessel. The precise mechanism underlying the atherosclerotic plaque growth is not well understood. Recent research has suggested that the interaction of platelets with the endothelial cells of the blood vessels is important in the development of the acute complications of the disease. Both of these cells secrete various signaling molecules and express adhesion molecules, which can influence the development of pathological states [3].

The general blood flow dynamic can be explained by Poiseuille's equation (derived from the law of mass conservation) and Bernoulli's equation (derived from the conservation of momentum) which are integrated into Navier-Stokes equation (NSE) for the determination of flow field [4]. However, the application of NSE to understand atherosclerosis may be quite challenging. Blood flow is pulsating in tapered elastic vessels that are connected in a branching network. Blood flow is unsteady, and is considered to be non-Newtonian [5]. To develop a complete model for blood flow in arteries, these effects should be taken into consideration. That is, one would have to use the full theory of fluid dynamics, which requires solving the NSE coupled with the dynamics of the compliant blood vessels [6].

Many factors involved in atherosclerosis are secondary and initiated due to several biomechanical and physiological cascading events. In order to understand atherosclerosis, the blood flow dynamics in the occluded region must be investigated. Such work will provide ways to develop novel techniques for understanding CHD.

Various procedures (e.g., angioplasty and stenting) are being applied in order to cure coronary occlusions. However, the treatment can be complicated, risky and the failure rate is high. Therefore, extensive research is being done to find alternative means of predicting and curing such disease [7], [8]. In bioinformatics and biological systems, computational techniques have been deployed to understand the molecular dynamics and their interaction which may assist in elucidating various pathways leading to abnormalities. Furthermore, hypothesis can be checked, corrected and revised based on simulated results and their correlation with actual data [9], [10].

In this paper, computer modeling and simulation are used to investigate the biomechanical processes underlying the mechanism by which platelets can be activated and consequently leading to platelet aggregation in atherosclerosis.

II. METHODOLOGY

The mechanism by which the blood flow profile is modified in the atherosclerosis region was examined here. Due to the complexity of the blood flow dynamics and its interaction with the blood vessel, it is difficult to develop the whole realistic model for the purpose of analysis. Therefore, a simplified version of blood flow is modeled in which we considered the following characteristics: (1) blood is an incompressible viscous Newtonian fluid; (2) blood flow is laminar, steady and non-pulsating and (3) arteries are rigid with no-slip boundaries.

The plaque is inhomogeneous and highly irregular structure made up from different substances such as fat deposits, white blood cells, red blood cells and platelets [2].We propose that the incremental build-up of plaque causes localized turbulences at this rough surface which produce regional stresses that can induce platelet activation. Here we investigate how the change in the plaque size at the stenotic region affects the blood flow dynamics leading to increased rate of platelet activation.

FlexPDE 5.0 computational fluid dynamics software was used to model blood flow dynamics in an occluded artery. To test our hypothesis, we found that FlexPDE 5.0 was both

flexible in designing blood flow model and solving 2D NSE (1) with a minimum level of programming.

$$\left.\begin{aligned} \rho\left(\frac{\partial u}{\partial t}+u\cdot\nabla u-f\right)-\mu\nabla^2 u+\nabla p=0 \\ \nabla\cdot u=0 \end{aligned}\right\} \qquad (1)$$

The first line of the equation represents the conservation of momentum, basically, the Newton's second law – in terms of fluid velocity vector u and pressure p. The second line represents the conservation of mass. The body force f is frequently absent, and the remaining parameters – fluid density (ρ) and viscosity (μ) are often constant [6].

We studied the effect of two different sizes of occlusions located on the inner wall of a channel (artery). In order to obtain a good contrast in the computational simulations, the plaque sizes were selected to be 1/5 (case 1) and 1/2 (case 2) the diameter of the channel. The flow, speed, pressure, velocity along the direction of the blood flow (u) and velocity in the direction perpendicular to the flow (v) were calculated to determine the blood flow dynamics in the stenotic region. The numerical solution of the flow field at Reynold's number (Re) = 10 was determined. The solution for the non-linearly coupled NSEs was obtained through an iterative procedure.

Fig.1 shows the finite element mesh generated by the FlexPDE 5.0 software. It is worth mentioning that the continuity error in the calculation of flow, pressure and velocity was automatically minimized by the ability of the software to dynamically recalculate and adjust the mesh size. This gave better simulation results at the stenotic region.

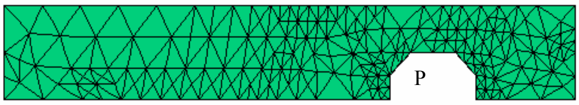

Fig. 1: A finite element mesh in an occluded vessel where the region labeled P represents the plaque. The total number of nodes and cells in the mesh were 2061 and 978 respectively.

III.RESULTS

Fig.2a shows the vector diagram for the profile of blood flow across an occluded artery for case 1. At the boundaries of the blood vessel, the fluid movement is relatively slow compared to the central region. This behavior can be adequately explained due to the non-slip boundary condition as expected for viscous fluids. As can be seen, the blood flow is suddenly disrupted at the stenotic region where the volume and direction of flow changes abruptly (represented by the arrows). These changes produce three distinct regions labeled A, B and C.

Closer examination of region A shows two blood streams at the lower part of the vessel approaching the plaque area. The flow rate of the first stream increases as it travels over the plaque while the flow rate of the second stream (adjacent to the artery wall), rapidly decreases with loss of energy leading to blood stagnation. Region B corresponds to the maximum flow rate as the blood passes over the plaque. At region C the flow rate is very low and the stagnation region is much larger as compared to region A.

Fig. 2b represents the speed of blood flow across the occluded artery. The colored contours provide a better illustration of the three regions mentioned above i.e., A, B and C. The influence on the speed due to the occlusion extends horizontally to approximately five times the diameter of the plaque along the flow direction. The region labeled X, just above the plaque, represents the highest speed. As the fluid leaves the stenotic region, the speed gradually decreases and reaches its steady state value.

On the other hand, we investigated the pressure profile characteristics in the vicinity of the occluded region. Fig. 2c shows a gradual increase in pressure as the blood moves away from the occlusion along the general direction of the flow. The highest pressure value is at region A due to the relatively low blood flow rate. It is worth noting that this region was also found to have high blood stagnation. As the blood flows over the plaque it picks up speed as the pressure begins to drop. Region C was found to represent the lowest pressure area.

Fig. 2d shows the velocity (u) of fluid particles in the x direction. At the top boundary of the vessel and surrounding the plaque, a thin layer represents near zero linear velocity of blood.

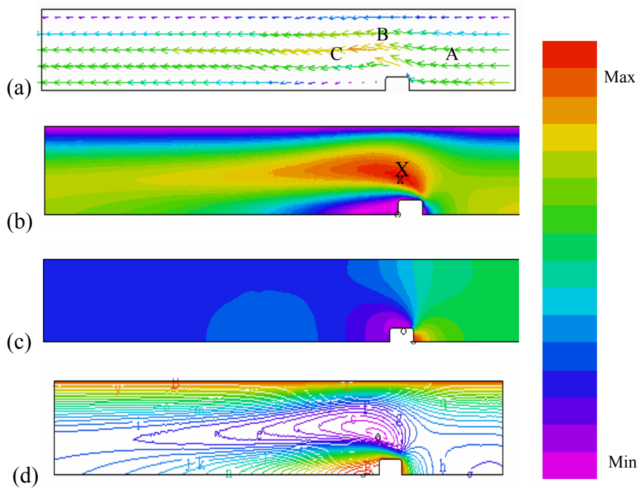

Fig. 2: Various plots for a low density fluid moving in a 2-D occluded channel. In computer simulation, the square shaped object represents a plaque (1/5 the diameter of the artery) located in the inner wall of an artery. The various plots are (a) flow, (b) speed, (c) pressure and (d) velocity in x-direction. The results were obtained with Re number = 10.

Fig. 3 shows the effect of increasing the size of the occlusion on the blood flow dynamics (case 2). The obtained results were more profound especially at the plaque region. The continuity errors in the numerical calculation were found to be large at the edges of the plaque. However, the results were unaffected due to the ability of the software to minimize the error.

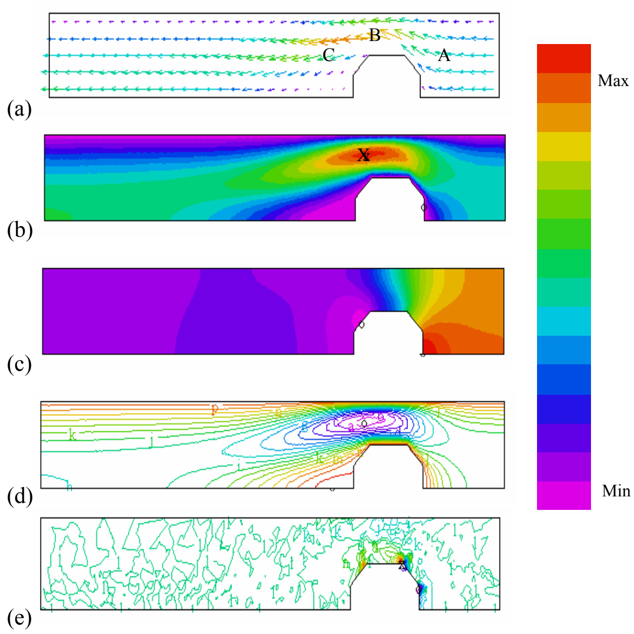

Fig. 3: Simulated results for a plaque size approximately half the diameter of the blood vessel. The general characteristics of blood flow are similar to the corresponding plots (a-d) in figure 2 but are more profound. Note that the continuity error was readjusted during simulation to obtain more accurate results (e).

IV. DISCUSSION

The pressure near the plaque region can be obtained from the general Bernoulli's equation (2).

$$p + \frac{1}{2}\rho V^2 + gz\rho = \text{constant (kJ/kg)} \quad (2)$$

Where P is the pressure, V is the velocity at a point, g is the gravitational force and z is the diameter of the channel [11]. Ignoring the gravitational term (gzρ = 0), we can determine the pressure differences at any two points (P1 and P2) (3).

$$P_1 + \frac{1}{2}\rho V_1^2 = P_2 + \frac{1}{2}\rho V_2^2 \quad (3)$$

The pressure decreases in correspond to the increase in the velocity as it approaches the plaque region. The blood flow dynamic becomes very complex especially at the boundaries of the plaque. The relatively high speed close to the boundaries causes a sudden increase in Re (4). Where Vm = mean fluid velocity (m/s), D = Diameter (m), ν = μ/ ρ = Kinematic viscosity of fluid (m2/s), μ is the dynamic viscosity and ρ corresponds to the density. A high blood velocity indicated in Re number provides an explanation of a possible turbulent flow at the plaque region. The roughness of the plaque surface will further enhance the localized turbulences.

$$\mathrm{Re} = \frac{V_m D}{\nu} \quad (4)$$

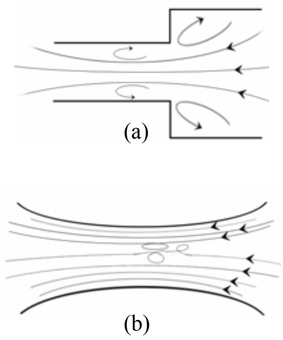

Fig. 4: Arrows representing the (a) back flow of blood due to the adverse pressure changes at the stenosis boundary and (b) showing the vortices at the center of the vessel.

As the blood flow interacts with the edge of the plaque, it encounters a strong adverse pressure gradient resulting in a region of backward flow (vortices and eddies) as shown in Fig.4. A turbulent boundary layer is formed around the plaque giving rise to additional shear stresses [6]. At the boundaries the fluid particles may circle around several times and hence experience a longer residence time in the stagnated region before continuing along the general flow of the blood (Fig. 4b).

Such behavior plays a crucial role in the events leading to platelet aggregation at the stenotic region. It is well known that shear stress is a major factor involved in platelet activating leading to blood clotting [6],[12]. The shear stress acting on the platelets is given by equation 5 and 6.

Where τlam is the laminar stress, dV/dy is the velocity gradient (ms-1/m), τturb = turbulent stress [13], [14].

$$\tau_{lam} = \mu \frac{dV}{dy} \quad (5)$$

$$\tau_{total} = \tau_{lam} + \tau_{turb} \quad (6)$$

The disruption of the integrity of the blood flow by the plaque results in a cascade of events including adhesion, shape change and aggregation. Each discoidal platelet transforms into a spiny sphere with multiple protruding pseudopodia that give the surface a highly irregular contour. Such structural transformational changes allow for enhanced interaction and adhesion [15],[16],[17].

The activation of platelets occurs in the thin boundary layer around the plaque where the blood flow is turbulent. Turbulence is a non-linear and chaotic state characterized by macroscopic mixing of fluid particles [6], [16]. It is believed that such behavior gives rise to collisions between platelets and other particles as well as between platelets and the plaque boundary. Thus, the probability of inelastic collisions increases the chance of platelet adhesion.

In this work we have investigated the dynamic behavior of blood flow as it passes over the atherosclerosis region using computer modeling and simulation. By solving NSE, areas were identified where pressure, speed and velocity changed rapidly giving rise to 'hot spots' (eddies and vortices). Such sites corresponded to regions for platelets activation and aggregation. Factors that culminate to the attachment of the platelets to the plaque are: (1) stagnation of the blood flow (2) roughness of the arterial wall and (3) increase in the surface area of the activated platelets.

Computational modeling of blood flow dynamics provides valuable tool for the explanation of the mechanisms involved in atherosclerosis and probably play an increasing role for developing new ways of curing coronary heart disease in the future.

V. REFERENCES

[1] A.C. Guyton and J. E. Hall, *Text Book of Medical Physiology,* 9th ed, Pennsylvania: W.B. Saunders Company, 1996, pp. 259-262.

[2] J.E. Freedman, "Molecular regulation of platelet-dependent thrombosis," *Circulation*, vol. 112**,** pp. 2725-2734, 2005.

[3] K.T. Tan and G.Y. Lip, "Platelets, atherosclerosis and the endothelium: New therapeutic targets," *Drugs*, vol. 12, pp. 1765-1776, 2003.

[4] M. Watanabe, R. Kikinis and C. Westin, "Level set-based integration of segmentation and Computational fluid dynamics for flow correction in phase contrast angiography," *Acad. Radiol*., vol. 10, pp. 1416-1423, 2003.

[5] F.G. Gijsen, F.N. Van de Vosse, and J.D. Janssen, "The influence of the non-Newtonian properties of blood on the flow in large arteries: Unsteady flow in a 90-degree curved tube," *J. Biomech.,* vol. 32, pp. 705-713, 1999

[6] M. Anand and K. R. Rajagopal, "A shear-thinning viscoelastic fluid model for describing the flow of blood," *Int. J. Cardiovas. Medic. Scien.,* vol. 4, pp. 59-68, 2004.

[7] L. Kury, S. Ziad, M. Salah and I. Haq, *"Atherosclerosis-targeted nanolipase buckyballs*," *Int. J. Sci. Res.,* vol. 16, 2006, in press.

[8] J.P. Ku, M.T. Draney, F.R. Arko *et al*. "In vivo validation of numerical prediction of blood flow in arterial bypass grafts," *Ann. Biomed. Engineerinig,* vol. 30, pp. 743-752, 2002.

[9] L. Kury and I. Haq, "*Simulation of hypoxia-induced SERCA2a pump blockage using nanotubes," Int. J. Sci. Res.,* vol. 16, 2006, in press.

[10] L. Kury and I. Haq, "Computer modeling and nanotechnology for investigating and improving cardiac cell function," *Proceeding of the second International Conference on Innovations in Information Technology*. Dubai: ITT, 2005.

[11] P.K. Kandu and I.M. Cohen**,** *Fluid mechanics,* 2nd ed., US: Academic press, 2002, pp. 110-114.

[12] N. Maalej and J. D. Folts, "Increased shear stress overcomes the antithrombic platelet inhibitory effect of aspirin in stenosed dog coronary arteries," *Circulation,* vol. 93, pp. 1201-1205, 1996.

[13] D. Cruz, F.N. Batista, and M. A. Bortolus, "Law of the wall formulation for recirculating flows," *J. Braz. Soc. Mech. Sci.*, vol. 22**,** 43-51, 2000.

[14] Z. Li and C. A. Kleinstreuer, "New wall stress equation for aneurysm-rupture prediction," *Ann. Biomed. Eng*., vol. 33**,** pp**.** 209-213, 2005.

[15] P.W. Longest and C. Kleinstreuer, "Numerical simulation of wall shear stress conditions and platelet localization in realistic end-to-side arterial anastomoses" *J. Biomech. Eng*., vol. 125, pp. 671-681, 2003.

[16] C.B. Reininger, R. Lasser, M. Rumatiz, C. Boger and L.Schweiberer, "Computational analysis of platelet adhesion and aggregation under stagnation point flow conditions" *Comput. Biol. Med.*, vol. 29, pp. 1-18, 1999.

[17] S. Kulkarni, S.M. Dopheide, C.L. Yap *et al.* A revised model of platelet aggregation. *J. Clin. Invest.*, vol. 105, pp. 783-791, 2000.